

# PATENT SPECIFICATION

(11) 1 596 383

- 383 (21) Application No. 50347/77 (22) Filed 2 Dec. 1977  
 386 (61) Patent of Addition to No. 1547452 dated 4 June 1976  
 386 (31) Convention Application No. 2655009  
 1596 (32) Filed 4 Dec. 1976 in  
 1596 (33) Federal Republic of Germany (DE)  
 1596 (44) Complete Specification published 26 Aug. 1981

1 (51) INT CL<sup>3</sup> C07D 413/12 A61K 31/42 31/44 31/425 31/565 C07D  
 409/12 419/12 (C07D 417/12 261/18 277/46 277/82)  
 (C07D 235/30) (C07D 409/12 333/36) (C07D 413/12  
 213/5 239/42 263/58) (C07D 419/12 261/18 291/04)

(52) Index at acceptance

C2C 1370 1372 1382 1384 1390 1416 1510 1530 1602 213 215 247  
 250 251 252 254 255 256 25Y 270 271 280 281 29X 29Y  
 30Y 313 314 31Y 332 337 342 34Y 351 352 364 36Y 579  
 604 621 624 62X 635 671 672 802 80Y AA KF KP KS KT

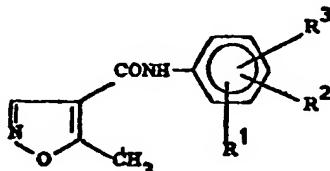


(54) ISOXAZOLE DERIVATIVES, PROCESS FOR THEIR  
 MANUFACTURE AND PREPARATIONS CONTAINING  
 THESE COMPOUNDS

5 (71) We, HOECHST AKTIENGESELLSCHAFT, a Body Corporate  
 organised according to the laws of the Federal Republic of Germany, of 6230  
 Frankfurt (Main) 80, Postfach 80 03 20, Federal Republic of Germany, do hereby  
 declare the invention for which we pray that a patent may be granted to us, and the  
 method by which it is to be performed, to be particularly described in and by the  
 following statement:—

This invention relates to isoxazole derivatives and is an improvement in, or  
 modification of, the invention of Patent No. 1,547,452.

10 Patent No. 1,547,452 describes and claims 5 - methyl - isoxazole - 4 -  
 carboxylic acid anilides of the general formula



15 in which R<sup>1</sup> and R<sup>2</sup>, which may be identical or different, each represents a  
 hydrogen atom; an alkyl group of 1, 2 or 3 carbon atoms, an alkoxy group of 1, 2 or  
 3 carbon atoms, an alkylthio group of 1, 2 or 3 carbon atoms, the alkyl groups of  
 which may be substituted partly or totally by identical or different halogen atoms,  
 for example, fluorine, chlorine, bromine or iodine atoms, or represents a halogen  
 atom, for example, a fluorine, chlorine, bromine or iodine atom, or represents a  
 nitro or cyano group or an alkoxy carbonyl group having 1, 2 or 3 carbon atoms in  
 the alkyl moiety,

20 R<sup>3</sup> represents an alkyl group of 1, 2 or 3 carbon atoms, an alkoxy group of 1, 2  
 or 3 carbon atoms, an alkylthio group of 1, 2 or 3 carbon atoms, the alkyl groups of  
 which may be substituted partly or totally by identical or different halogen atoms,  
 for example, fluorine, chlorine, bromine or iodine atoms, or represents a halogen  
 atom, for example, a fluorine, chlorine, bromine or iodine atom, or represents a  
 nitro or cyano group or an alkoxy carbonyl group having 1, 2 or 3 carbon atoms in  
 the alkyl moiety; or represents a phenyl group which may carry one or two  
 25 substituents selected from fluorine, chlorine, bromine and iodine atoms, alkyl  
 groups of 1, 2 or 3 carbon atoms and alkoxy groups of 1, 2 or 3 carbon atoms, or a  
 phenoxy group which may carry one or two substituents selected from fluorine,  
 chlorine, bromine and iodine atoms, alkyl groups of 1, 2 or 3 carbon atoms and  
 30 alkoxy groups of 1, 2 or 3 carbon atoms; or in which R<sup>1</sup> stands for a hydrogen atom,  
 and R<sup>2</sup> and R<sup>3</sup> together represent a methylenedioxy group or, together with the  
 phenyl ring, to which they are linked, represent a naphthalene ring; with the

5

10

15

20

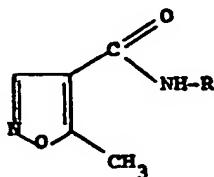
25

30

proviso that R<sup>3</sup> does not represent a methyl group when R<sup>1</sup> and R<sup>2</sup> both represent hydrogen atoms.

We have now found that pharmacological properties are also shown by 5 - methylisoxazole - 4 - carboxylic acid amides of the general formula

5



(I)

5

10

15

20

25

30

35

10

15

20

25

30

35

40

in which R represents a mononuclear, binuclear or trinuclear, unsaturated heterocyclic radical having in the ring system 3 to 13 carbon atoms and one, two, three or four hetero atoms selected from oxygen, sulphur and nitrogen, one of which at most is other than nitrogen, which ring system is unsubstituted or substituted by one or more substituents, preferably by one, two or three substituents selected from alkyl and alkoxy radicals each having one, two or three carbon atoms, by halogen atoms, i.e. fluorine, chlorine, bromine and iodine atoms, nitro, hydroxy and carboxy groups, unsubstituted and substituted carbamoyl radicals and oxo groups. Preferably, if there is more than one substituent, the substituents are the same.

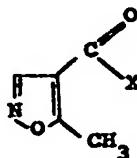
The present invention also provides a salt, especially a physiologically tolerable acid addition salt, of a compound of the general formula I.

The ring system may include a carbocyclic ring or rings, provided it contains at least one heterocyclic ring. The rings may be aromatic or non-aromatic and usually all are unsaturated.

Suitable radicals represented by R are, for example, thienyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, thiazolyl, thiazolinyl, oxazolyl, thiadiazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolyl, pyrazolyl, acridinyl and tetrazolyl radicals, each of which may be unsubstituted or substituted as specified.

Preferred compounds are those of the general formula I in which R represents a pyridyl radical which is unsubstituted or substituted by one, two or three of the same or different halogen atoms, i.e. fluorine, chlorine, bromine and iodine atoms, or represents a pyrimidinyl radical which is unsubstituted or substituted once, twice or three times by a (C<sub>1</sub>-C<sub>3</sub>)-alkyl radical and/or by the oxo group, or a thiazolyl radical which is unsubstituted or substituted by a nitro group.

The present invention also provides a process for the preparation of a compound of the general formula I or a salt thereof, which comprises reacting a 5 - methylisoxazole - 4 - carboxylic acid derivative of the general formula



(II)

35

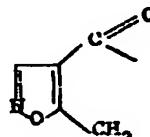
in which X represents

a) a halogen atom, preferably a chlorine or bromine atom;

b) a YO-group, in which Y represents

(i) a phenyl radical which is unsubstituted or substituted by one, two or three substituents selected from fluorine, chlorine, bromine and iodine atoms, and methyl, ethyl, methoxy, ethoxy or trifluoromethyl, nitro and cyano groups, or

(ii) the acyl radical corresponding to the formula (II) that is



(II\*)

40

45

or

45

c) a ZO—CO—O-group in which Z represents a ( $C_1$ — $C_4$ )-alkyl radical, a benzyl radical or a phenyl radical; or another reactive functional derivative of the carboxylic acid corresponding to the general formula II, with an unsaturated heterocyclic amine of the general formula

5

 $H_2N—R$ 

(III)

5

in which R has the meaning given above, or with a salt thereof.

Preferably, a substituted phenyl radical Y contains one substituent or two or three of the same substituents.

10

The reaction is advantageously carried out in a dispersing agent or a solvent that is inert towards the reactants. Suitable polar solvents that may be used are, for example, nitriles, e.g. acetonitrile; ethers, e.g. diethyl ether, tetrahydrofuran or dioxan; and alcohols, e.g. methanol, ethanol, propanol or isopropanol. Non-polar solvents, e.g. benzene, toluene and cyclohexane, may also be used.

15

Preferably the compound of the general formula II is the carboxylic acid chloride. It is advantageous in this case for the reaction to be carried out in the presence of an acid-binding agent, e.g. potassium or sodium carbonate, an alkali metal hydroxide, alkaline earth metal hydroxide, alkali metal alcoholate or alkaline earth metal alcoholate, an organic base, for example triethylamine, pyridine, picoline or quinoline or the amine reactant used in excess, at temperatures of from 0 to 160°C, preferably from 20 to 80°C. The reaction time may be from a few minutes to two hours.

20

A 5 - methylisoxazole - 4 - carboxylic acid derivative of the general formula II required as starting material may be obtained in accordance with the method described in German Patent No. 634 286. In this method ethoxymethyleneacetoacetic ester is reacted with hydroxylamine to form the 5 - methylisoxazole - 4 - carboxylic acid ester, the ester is hydrolysed under acid conditions, preferably with a mixture of glacial acetic acid and concentrated hydrochloric acid in the ratio 1:1, and the 5 - methylisoxazole - 4 - carboxylic acid formed is converted according to a customary method into a carboxylic acid halide, ester or mixed anhydride.

25

The following are examples of carboxylic acid derivatives of the general formula II:

5 - methylisoxazole - 4 - carboxylic acid phenyl esters, especially the 2,4-dichlorophenyl ester of the 2,4,6-trichlorophenyl ester; and

30

5 - methylisoxazole - 4 - carboxylic acid anhydrides, especially those in which X represents the methoxycarbonyloxy radical, the ethoxycarbonyloxy radical, the phenoxy carbonyloxy radical or the benzyloxycarbonyloxy radical.

35

The compounds according to the invention of the general formula I are generally substances that are readily crystallisable. They may be converted into acid addition salts, preferably physiologically tolerable acid addition salts, for example with strong acids, e.g. hydrohalic acids, especially hydrochloric acid, sulphuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulphonic acid or cyclohexylamidosulphonic acid.

40

The 5 - methylisoxazole - 4 - carboxylic acid amides of the general formula I and their physiologically tolerable salts have useful pharmacological properties. In particular they exhibit antiphlogistic, antipyretic and analgesic properties. Their toxicity is low, and their compatibility with the stomach is good.

45

Accordingly, the present invention provides a pharmaceutical preparation, which comprises a compound of the general formula I or a physiologically tolerable salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier. Preferably the preparation is in dosage unit form.

The following Examples illustrate the invention:

1. N - (5 - bromo - 2 - pyridyl) 5 - methylisoxazole - 4 - carboxamide of the general formula I.

50

a) A solution of 0.05 mole of 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) (7.3 g) in 20 ml of tetrahydrofuran is added dropwise at room temperature, while stirring, to 0.1 mole of 2-amino-5-bromopyridine of the formula (III) (17.3 g) dissolved in 200 ml of tetrahydrofuran. After stirring for a further 10 minutes, the precipitate formed is filtered off and the filtrate is evaporated to dryness under reduced pressure. 13.6 g (96% of the theoretical yield) of a colourless crystalline product are obtained; melting point from ethanol: 168—169°C.

10

15

20

25

30

35

40

45

50

55

60

- b) 0.1 mole of 2-amino-5-bromopyridine of the formula (III) (17.3 g) and 0.1 mole of 2,4-dichlorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) (27.2 g) dissolved in 150 ml of tetrahydrofuran are refluxed for 75 minutes. The solution is then brought to dryness under reduced pressure and the oily residue is digested with cyclohexane.
- After decanting, the residue is dissolved in 300 ml of chloroform and shaken with 200 ml of 2N hydrochloric acid.
- The chloroform phase is washed with water until neutral, dried, and brought to dryness under reduced pressure. 21.4 g (76% of the theoretical yield) of a crystalline product are obtained; melting point after recrystallisation from ethanol: 168 to 169°C.
- c) 0.1 mole of 2-amino-5-bromopyridine of the formula (II) (17.3 g) and 0.1 mole of benzyloxycarbonyl 5 - methylisoxazole - 4 - carboxylate of the formula II (26.1 g), dissolved in 200 ml of tetrahydrofuran, are refluxed for 90 minutes. The mixture is brought to dryness under reduced pressure and the residue is digested with cyclohexane. After decanting, the residue is dissolved in 300 ml of chloroform and shaken with 200 ml of 2N hydrochloric acid. The chloroform phase is washed with water until neutral, dried and brought to dryness under reduced pressure. In this manner 20.6 g (73% of the theoretical yield) of a crystalline product are obtained; melting point after recrystallisation from ethanol; 168 to 169°C.
- In accordance with the process described above:
- N-(3-pyridyl) 5 - methylisoxazole - 4 - carboxamide hydrochloride of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 3-aminopyridine of the formula (III),
- N-(4-methyl-2-thiazolyl) 5 - methylisoxazole - 4 - carboxamide hydrochloride of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 2 - amino - 4 - methylthiazole of the formula (III),
- N-(4-pyridyl) 5 - methylisoxazole - 4 - carboxamide hydrochloride of the formula (I) is obtained by reacting 2,4-dichlorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - amino - 4 - pyridine of the formula (III),
- N -(4 - chloro - 2 - benzothiazolyl) 5 - methylisoxazole - 4 - carboxamide of the formula I is obtained by reacting 2,4-dichlorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - amino - 4 - chlorobenzothiazole of the formula (III),
- N-(2-pyridyl) 5 - methylisoxazole - 4 - carboxamide hydrochloride of the formula (I) is obtained by reacting 2,4-dichlorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula II with 2-aminopyridine of the formula (III),
- N - (5 - bromo - 2 - pyridyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 2 - amino - 5 - bromopyridine of the formula (III),
- N - (1,3 - dimethyl - 2,4 - dioxo - 1,2,3,4 - tetrahydro - 6 - pyrimidinyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 6 - amino - 1,3 - dimethyl - 2,4 - dioxo - 1,2,3,4 - tetrahydropyrimidine of the formula (III),
- N - (5 - nitro - 2 - thiazolyl) 5 - methylisoxazole - 4 - carboxamide hydrochloride of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 2 - amino - 5 - nitrothiazole of the formula (III),
- N - (2 - thiazolin - 2 - yl) 5 - methylisoxazole - 4 - carboxamide hydrochloride of the formula (I) is obtained by reacting 2,4-dichlorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - amino - 2 - thiazoline of the formula (III),
- N-(2-benzothiazolyl) 5 - methylisoxazole - 4 - carboxamide hydrochloride of the formula (I) is obtained by reacting benzyloxycarbonyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - aminobenzothiazole of the formula (III),
- N - (2 - benzimidazolyl) 5 - methylisoxazole - 4 - carboxamide hydrochloride of the formula (I) is obtained by reacting 2,4 - dichlorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - amino - benzimidazole of the formula (III),
- N - (5 - chloro - 2 - benzoxazolyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting benzyloxycarbonyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - amino - 5 - chlorobenzoxazole of the formula (III),

N - (5 - nitro - 2 - pyridyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 2,4-dichlorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - amino - 5 - nitropyridine of the formula (III),

N - (3,5 - dibromo - 2 - pyridyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting benzyloxycarbonyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - amino - 3,5 - dibromopyridine of the formula (III),

N - (5 - chloro - 2 - pyridyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 2 - amino - 5 - chloropyridine of the formula (III),

N - (2 - chloro - 3 - pyridyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 3 - amino - 2 - chloropyridine of the formula (III).

N - (4 - methyl - 3 - thiienyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 3 - amino - 4 - methylthiophene of the formula (III).

N - (6 - methoxy - 2 - benzothiazolyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 2,4-dichlorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - amino - 6 - methoxybenzothiazole of the formula (III),

N - (5 - chloro - 2 - thiazolyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 2,4-dichlorophenyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 2 - amino - 5 - chlorothiazole of the formula (III),

N - (2 - methoxy - 5 - pyridyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 5 - amino - 2 - methoxypyridine of the formula (III),

N - (6 - ethoxy - 2 - benzothiazolyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting benzyloxycarbonyl 5 - methylisoxazole - 4 - carboxylate of the formula (II) with 6 - ethoxy - 2 - aminobenzothiazole of the formula (III),

N - (5 - bromo - 2 - thiazolyl) 5 - methylisoxazole - 4 - carboxamide of the formula (I) is obtained by reacting 5 - methylisoxazole - 4 - carboxylic acid chloride of the formula (II) with 2 - amino - 5 - bromothiazole of the formula (III).

40 TABLE I:  
5-Methylisoxazole-4-carboxylic acid amides of the  
formula I

5

10

15

20

25

30

35

40

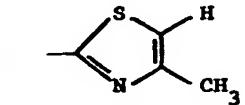
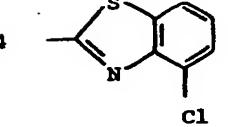
| No. | R   | Melting point °C             |
|-----|---|------------------------------|
| 1   |  . HCl | 250-252 (with decomposition) |
| 2   |  . HCl | 221-223                      |
| 3   |  . HCl | 210-215 (with decomposition) |
| 4   |  . HCl | 218-220                      |

TABLE I continued

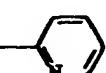
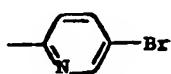
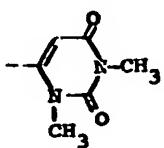
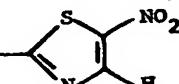
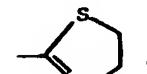
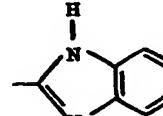
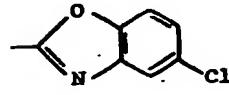
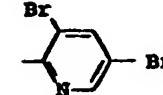
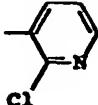
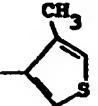
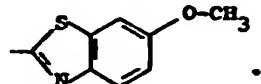
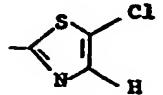
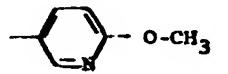
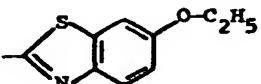
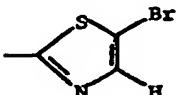
| No. | R   | Melting point °C                    |    |
|-----|---|-------------------------------------|----|
| 5   |    | 239-242                             |    |
| 6   |    | 168-169                             |    |
| 5   |    | 192-194                             | 5  |
| 8   |    | HCl<br>151-154                      |    |
| 9   |    | HCl<br>260-265 (with decomposition) |    |
| 10  |   | HCl<br>234-237 (with decomposition) |    |
| 11  |  | HCl<br>230-235 (with decomposition) |    |
| 10  |  | HCl<br>170-175 (with decomposition) | 10 |
| 13  |  | 202-203                             |    |
| 14  |  | 165-167                             |    |
| 15  |  | 165-168                             |    |

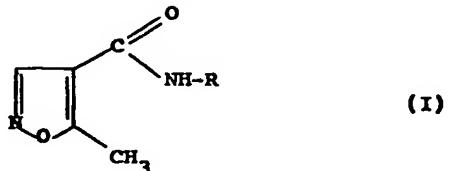
TABLE I continued

| No. | R   | Melting point °C  |                                |
|-----|---|---|--------------------------------|
| 16  |    | 112-114 (with decomposition)  |                                |
| 17  |    | 113-115   |                                |
| 5   | 18  |  + HCl | 215-219 (with decomposition) 5 |
| 19  |    | 210-220 (with decomposition)  |                                |
| 20  |    | 154-156 (with decomposition)  |                                |
| 21  |   | HCl 216-221 (with decomposition)  |                                |
| 22  |  | 203-211 (with decomposition)  |                                |

10

## WHAT WE CLAIM IS:—

1. A compound of the general formula



15

in which R represents a mononuclear, binuclear or trinuclear, unsaturated heterocyclic radical having in the ring system 3 to 13 carbon atoms and one, two, three or four hetero atoms selected from oxygen, sulphur and nitrogen, one of which at most is other than nitrogen, which ring system is unsubstituted or substituted by one or more substituents selected from alkyl and alkoxy radicals each having one, two or three carbon atoms, halogen atoms, nitro, hydroxy and carboxy groups, unsubstituted and substituted carbamoyl radicals and oxo groups.

15

2. A compound as claimed in claim 1, wherein the ring system is unsubstituted or contains up to 3 substituents.

3. A compound as claimed in claim 2, wherein R represents a pyridyl radical which is unsubstituted or substituted by 1 to 3 of the same or different halogen atoms; a pyrimidinyl radical which is unsubstituted or substituted by 1 to 3 of the same or different substituents selected from ( $C_1$ — $C_3$ )-alkyl radicals and oxo groups; or a thiazolyl radical which is unsubstituted or substituted by a nitro group.

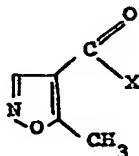
4. A salt of a compound as claimed in any one of claims 1 to 3.

5. A physiologically tolerable salt of a compound as claimed in any one of claims 1 to 3.

10 6. A compound as claimed in claim 1, which is listed in any of the Examples and Table herein.

7. A process for the preparation of a compound as claimed in claim 1 or a salt thereof, which comprises reacting a compound of the general formula

15



(II)

15

in which X represents

a) a halogen atom;

b) a YO-group, in which Y represents

(i) a phenyl radical which is unsubstituted or substituted by one, two or three of the same or different substituents selected from fluorine, chlorine, bromine and iodine atoms, and methyl, ethyl, methoxy, ethoxy, trifluoromethyl, nitro and cyano groups, or

(ii) the acyl radical corresponding to the formula II; or

20 c) a ZO—CO—O-group in which Z represents a ( $C_1$ — $C_4$ )-alkyl radical, a benzyl radical or a phenyl radical; or another reactive functional derivative of the carboxylic acid corresponding to the general formula II with an unsaturated heterocyclic amine of the general formula



(III)

30

in which R has the meaning given in claim 1 or with a salt thereof, and, if desired, converting a compound of the general formula I formed into a salt.

35 8. A process as claimed in claim 7, wherein the compound of the general formula II is the chloride and the reaction is carried out in the presence of an acid-binding agent.

9. A process as claimed in claim 8, wherein the reaction is carried out at a temperature in the range of from 20 to 80°C.

35

10. A process as claimed in claim 7, wherein the compound of the general formula II is the 2,4-dichlorophenyl ester, the 2,4,6-trichlorophenyl ester or an anhydride in which X represents the methoxycarbonyloxy, ethoxycarbonyloxy, phenoxy carbonyloxy or benzyloxycarbonyloxy radical.

40

11. A process as claimed in claim 7, carried out substantially as described in any one of the Examples herein.

45

12. A compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 7 to 11.

13. A salt of a compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 7 to 11.

14. A physiologically tolerable salt of a compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 7 to 11.

5

10

20

25

30

35

40

45

15. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 3, 5, 6, 12 and 14, in admixture or conjunction with a pharmaceutically suitable carrier.

16. A pharmaceutical preparation as claimed in claim 15, which is in dosage unit form.

5

ABEL & IMRAY,  
Chartered Patent Agents,  
Northumberland House,  
303—306 High Holborn,  
London, WC1V 7LH.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1981  
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from  
which copies may be obtained.